## REMARKS

Claims 1-39 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the outstanding Office Action.

1. The Examiner has withdrawn from consideration claims 4, 10-13, 41-46, as being drawn to non-elected inventions. Pursuant to the allowance of claim 1, Applicants request examination of claims 4, 10-13, 41-46 as required under MPEP § 809.04.

2. The Examiner has objected to claim 17 under 37 CFR 1.75(c) as being of improper form because a multiple dependent claim should refer to other claims in the alternative only. Claim 17 has been amended so as to refer to other claims in the alternative. Applicants respectfully request reconsideration and withdrawal of the objection.

3. The Examiner has withdrawn the rejection of claim 39. Applicants gratefully acknowledge this action.

4. Applicants note with appreciation that the Examiner has withdrawn the rejection of claims 1-3, 5, 7, 14-18, 25-31 under 35 U.S.C. 112, first paragraph.

5. Claims 26-34 are rejected under 35 U.S.C. 112, 1st paragraph, for containing subject matter which was not described in the specification in such a way as to enable a skilled artisan to make or use the invention. Applicants traverse the rejections.

At issue is whether a skilled artisan, having read the instant application, would have been able to make and use what is claimed in claims 26-34 without undue experimentation. Claim 26, the independent claim in the rejected claim set, is directed to a method for treating a 5-HT receptor-mediated disorder in an animal, comprising co-administering to the animal an amount of a nefazodonoid sufficient to inhibit a 5-$HT_2$ receptor activity to a therapeutically effective extent, and an amount of a serotonin reuptake inhibitor (SRI) sufficient to inhibit serotonin reuptake to a therapeutically effective extent, wherein the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI. The Examiner asserts that the specification provides no example or support for the claimed critical limitation for the combination of a nefazodonoid and any

serotonin reuptake inhibitor wherein the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI.

Applicants respectfully disagree and direct the Examiner's attention to page 6, 2nd paragraph of the specification wherein it is reported that an optimum therapeutic dosage of nefazodone between 300 and 600 mg/day achieves the therapeutic effects resulting from 5-HT receptor antagonism and serotonin reuptake inhibition. One skilled in the art would recognize that therapeutically effective dosages typically meet or exceed the $ED_{50}$ of the drug, and Applicants specify on page 6, paragraph 2, that in certain embodiments the nefazodone dosage is less than half the $ED_{50}$ for serotonin reuptake, and more preferably less than one tenth the $ED_{50}$ for serotonin reuptake. Additionally, the specification on page 4, second paragraph states that the single dosage form contains less than 100 mg of a nefazodonoid, such as single dosage forms of equal to or less than 50, 40, 25, or even 10 mg (page 3, third whole paragraph). Applicants respectfully point out that the nefazodone dosages specified for these embodiments (<10-50mg) roughly correspond to one-tenth the therapeutically effective dosage of nefazodone reported as being optimal for 5-HT receptor antagonism and serotonin reuptake inhibition. In light of these disclosures and examples, Applicants assert that one of skill in the art would find sufficient guidance to co-administer a nefazodonoid and any serotonin reuptake inhibitor wherein the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI.

In addition, although the Examiner asserts that the specification provides no example or support for the combination of a nefazodonoid and any serotonin reuptake inhibitor wherein the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI, on page 5 of the outstanding Office Action, the Examiner maintains that the secondary reference MHi Ask the Expert teaches 50 mg of nefazodone, and asserts that this amount meets "the requirement in the specification that the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI." This position appears to contradict the position that one of skill in the art would require undue

experimentation to identify a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI.

The Examiner also acknowledges the determination of dosage involves parameters that vary between patients: age, weight, medical history, etc. However, the MPEP recognizes that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (MPEP 2164.06). To begin with, the specification provides a guideline (see pages 26 and 31-32) for prophylactic or therapeutic doses of an SRI and a nefazodonoid to be administered to a patient. The specification provides guidance on which compounds are useful as nefazodonoids or SRIs; provides specific examples of nefazodonoids and SRIs; gives guidance as to how much of a nefazodonoid to administer vis-à-vis the SRI; and provides general dosage regimens for the co-administration of a nefazodonoid and an SRI. The particulars of determining how much of each to give to any given patient is an optimization exercise that is routine in the medical arts, especially for treating emotional and behavioral conditions such as depression, and does not constitute undue experimentation. For example, it is common practice in the medical arts to start a treatment with a low dosage of a therapeutic and to slowly elevate the dosage until the desired effect is observed (see exhibits A and B, printouts from the websites http://www.mhsource.com/expert/exp1062397g.html and http://www.thebody.com/Forums/AIDS/Cancer/Archive/lymphomas/Q112532.html, respectively in addition to Exhibit A from Applicants reply filed January 15, 2004). This practice of "start low, go slow" exemplifies the type of empirical experimentation routinely performed by practitioners of the medical arts in regard to determining optimal dosages on a individual patient basis using medications of the type at issue here. Applicants assert that general guidelines for initial dosages are presented and that one of ordinary skill in the arts would readily be able to carry out the routine experimentation to arrive at suitable doses of the instant invention. Although the Examiner argues there is no "nexus" established between a particular 5-HT receptor-mediated disorder and clear dosages of the two active drugs, Applicants assert that the use of both nefazodonoids and SRIs individually is well documented in the art, including standard dosages for treating particular diseases with particular medications, and that it is within the ability of a medical practitioner to adjust these doses for a particular patient in light of the

teachings of the specification without undue experimentation. Applicants respectfully request reconsideration and withdrawal of the objection.

6. Claims 1-3, 5-9 and 14-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fava M., J. Clin. Psychiatry, in view of the web site MHi Ask the Expert-SSRI and Nefazodone. Applicants traverse the rejection.

Claim 1 is directed to a pharmaceutical preparation comprising a nefazodonoid and a serotonin reuptake inhibitor in a pharmaceutically acceptable excipient. Claim 19 sets forth a pharmaceutical preparation comprising, in a single dosage form, a mixture of a nefazodonoid and a fluoxetinoid. Claim 25 recites a kit comprising a nefazodonoid and a selective serotonin reuptake inhibitor in single dosage form, each in a pharmaceutically acceptable excipient, and instructions for co-administering the nefazodonoid and selective serotonin reuptake inhibitor for treating a serotonin-mediated disorder. Claim 26 is directed to a method for treating a 5-HT receptor-mediated disorder in an animal by co-administering to the animal an amount of a nefazodonoid sufficient to inhibit a $5\text{-HT}_2$ receptor activity to a therapeutically effective extent, and an amount of a serotonin reuptake inhibitor (SRI) sufficient to inhibit serotonin reuptake to a therapeutically effective extent, wherein the nefazodonoid is administered at a dosage below the necessary dosage to inhibit serotonin reuptake to a therapeutically effective extent in the absence of the SRI. Claim 35 recites a method for treating depression in a human patient by administering to the patient (a) a nefazodonoid selected from nefazodone, hydroxynefazodone, or oxonefazodone in an amount of 100 mg or less per day, and (b) a fluoxetinoid selected from fluoxetine or norfluoxetine in an amount sufficient to inhibit serotonin reuptake to a therapeutically effective extent. Claim 39 sets forth a method for preparing a pharmaceutical preparation by combining a nefazodonoid, a fluoxetinoid, and a pharmaceutically acceptable excipient in a composition suitable for simultaneous administration of the nefazodonoid and the fluoxetinoid to a patient.

As has been made of record, even though Fava mentions augmentation of an SRI with nefazodone, this reference actually teaches away from using such a combination on grounds that it can cause what is known as a serotonin syndrome, worsening anxiety and irritability, and potential drug interactions. "A prima facie case of obviousness can be rebutted if the

applicant...can show that the art in any material respect `taught away' from the claimed invention...A reference may be said to teach away when a person of ordinary skill, upon reading the reference...would be led in a direction divergent from the path that was taken by the applicant." (See MPEP 1504.03 quoting In re Haruna, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001.).

Applicants assert that one of ordinary skill in the art, having read Fava, would hesitate to co-administer a nefazodonoid with an SRI in view of three disclosed disadvantages: serotonin syndrome, worsening anxiety and irritability, and potential drug interactions. The Examiner argues that Fava reports anecdotal evidence that combination of nefazodone with an SSRI has been shown to mitigate sexual dysfunction related to SSRI's, and thus one of ordinary skill in the art would be motivated to pursue the combination therapy despite the risks. However, in the face of this one asserted "advantage" of combining nefazodone and SSRI according to Fava. Applicants submit that Fava nonetheless teaches away from such a combination by reporting *three* disadvantages of the combination, including serotonin syndrome, worsening anxiety and irritability, and potential drug interactions. Moreover, Fava reports alternative preferred approaches to managing SSRI-induced sexual dysfunction: other drug/SSRI combinations including dopaminergics, mirtazapine, and the "top choice" bupropion, all of which are said to manage SSRI-induced sexual dysfunction. Indeed, Fava reports that bupropion was the "top choice of the psychiatrists participating in the Massachusetts General Hospital Augmentation Strategy Survey for Refractory Depression." None of these alternatives taught by Fava is said to possess the threat of potential serotonin syndrome attached to the nefazodone/fluoxetine combination. Indeed, it is Applicants who discovered that by using dosages as recited in the pending claims, such side effects can be minimized or eliminated altogether.

Similarly, the Mhi reference also cautions against the simultaneous administration of nefazodone and SSRI, citing the serotonin syndrome risk. Accordingly, the cited references do not support a prima facie case of obviousness for the presently claimed methods and compositions, because both teach away from the simultaneous administration of nefazodone and SSRI.

Furthermore, the Mhi reference on its face does more to undermine the simultaneous administration of a nefazodonoid and an SRI than it does to support the obviousness of such an administration. That the reference lacks a reasonably enabling disclosure is evidenced plainly in its acknowledgement that to the best knowledge of the responder that "there are no published studies on the combination of an SSRI with nefazodone." The reference only offers that a nefazodone/SRI combination is one of several combinations that one might try. However, the reference does not appear to endorse this regimen because the advice-giver later states "frankly, though, I've had better results combining SSRIs with dopaminergic agents, such as methylphenidate." The MHi reference clearly favors one of the alternatives advanced by Fava. Additionally, the MHi reference does not evince a strong likelihood for the chance of success in administering the nefazodone/SSRI combination of 50 mg nefazodone and 5 mg fluoxetine. The statement "Of course, in refractory depression, we do sometimes take calculated risks" highlights both the perceived dangers associated with the nefazodone/SSRI combination (from serotonin syndrome) as well as the perceived diminished probability of success. However, a reasonable expectation of success is required to prove a *prima facie* case of obviousness (MPEP § 2143.02), and the MHi reference precludes this expectation.

Since both references, taken together or separately, teach away from implementing the claimed method by warning of numerous disadvantages and provide no reasonable expectation of success for the presently claimed subject matter, Applicants submit that these references fail to render the claimed subject matter obvious. Indeed, Applicants assert that one of ordinary skill in the art after reading these references would be dissuaded from trying the presently claimed subject matter – indeed, would be induced to try one of the alternative preferred solutions – and certainly would have no reason to predict the particular advantages identified by Applicants. In light of the arguments presented above, Applicants respectfully request removal of this rejection.

## CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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